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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/081,872	02/21/2002	Walter Callen	09010-108001	9897

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EXAMINER	
PROUTY, REBECCA E	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 07/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/081,872	CALLEN ET AL.	
	Examiner	Art Unit	
	Rebecca E. Prouty	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *74,108,112-116 and 118-121* is/are withdrawn from consideration.

5)☒ Claim(s) *2-4* is/are allowed.

6)☒ Claim(s) *1,6-12,14-17,47,48,75-80,84-86,88,89,92,93,102-107 and 122-135* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/05, 4/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-4,6-12,14-17,47,48,74-80,84-86,88,89,92,93,102-108,112-116 and 118-135.

Claims 5, 13, 18-46, 49-73, 81-83, 87, 90-91, 94-101, 109-111, and 117 have been canceled. Claims 1-4, 6-12, 14-17, 47, 48, 74-80, 84-86, 88, 89, 92, 93, 102-108, 112-116, 118-124 and newly presented claims 125-135 are still at issue and are present for examination.

Applicants' arguments filed on 4/7/05, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claims 74, 108, 112-116 and 118-121 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction requirement in the response filed 6/23/03. Claims 1-4, 6-12, 14-17, 47, 48, 75-80, 84-86, 88, 89, 92, 93, 102-107, 122-124 and newly presented claims 125-135 are examined herein.

Claim 48 is objected to because of the following informalities: the word "and" should be inserted following "claim 1, 10, or 12;". Appropriate correction is required.

Claims 12, 14-17, 48, 102-107, 128, 129, 134, and 135 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly

claim the subject matter which applicant regards as the invention.

Claim 12 (from which claims 48, and 102-107 depend) is confusing in the recitation of "wherein the sequence encodes a polypeptide having alpha amylase activity" as it is unclear to which sequence "the sequence" refers. The claim recites "a sequence" in lines 1-2, and twice in line 3 such that it is not clear to which of these the later reference refers.

Claims 14, 15, 134 and 135 are indefinite in the recitation of "nucleic acid of claim 1, wherein the sequence identity" as it is unclear if "the sequence identity" refers to the nucleotide sequence identity of part (a) of claim 1 or the amino acid sequence identity of part (b) of claim 1. For purposes of examination it will be presumed to refer to both of these.

Claim 16 is indefinite as the phrase "the sequence comparison algorithm" lacks antecedent basis in claim 1 as amended.

Claims 17, 128, and 129 are confusing in the recitation "wherein the probe can identify or isolate an amylase-encoding gene by hybridizing to the gene..." as it is unclear how one can distinguish functional capabilities of a nucleic acid by hybridization as hybridization is a purely structural phenomenon; i.e., hybridization occurs between any two nucleic

acids which are sufficiently similar to each other to bind under the conditions of the hybridization reaction. Since even single changes to a nucleic acid sequence can result in the loss of activity of the encoded protein and conversely very different sequences structurally can encode proteins having the same activity it is unclear how an alpha amylase encoding gene can be distinguished from all sequences which do not encode an alpha amylase merely by hybridization. As such the recitation "identify or isolate an amylase-encoding gene by" has been given no patentable weight.

Claims 10-12, 17, 48, 75-80, 84-86, 88, 89, 92, 93, 102-107, 128, 129 and 131-133 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is explained in the previous Office Action.

Applicants submit that the claimed invention is sufficiently described in the specification so that one of ordinary skill in the art would be able to ascertain the scope of the claims with reasonable clarity and recognize that applicants were in possession of the claimed invention.

Applicants argue that describing a genus of polynucleotides in terms of physicochemical properties (e.g., a % sequence identity to an exemplary nucleic acid or polypeptide, e.g., SEQ ID NO:125 or SEQ ID NO:126 or stringent hybridization to an exemplary nucleic acid e.g., SEQ ID NO:125) and function (e.g., encoding a polypeptide having alpha amylase activity) satisfies the written description requirement of section 112, first paragraph. The examiner acknowledges that this is true where there is a sufficient correlation between the claimed structural and functional limitations. For example where the genus includes only nucleic acids which are highly structurally similar **over the entire portion of the disclosed species necessary for the recited function**, a single disclosed species would be likely be representative of the entire genus as the genus would not be diverse in either structure or function. However, where the recited structural feature(s) are not correlated to the recited functional features this would not be true as the single species would not be representative of the diversity of structures within the genus. It should be noted that all claims which recite genera in which the recited structural feature(s) are correlated to the recited functional features (i.e., claims which recite structural identity over the entire sequence of SEQ ID NOS:125 or 126 and encode proteins having alpha amylase

activity) have not been included in the instant rejection. All of the rejected claims on the other hand recite genera that either have no functional limitation at all (i.e., claims 17, 75-80, 84-86, 88, 89, 92, 93, 128, and 129) or recite only structural feature(s), such as high structural homology to fragments of SEQ ID NOS:125 or 126 that do not necessarily encode alpha amylases within the recited fragment, that are not correlated to the recited alpha amylase activity (i.e., claims 10-12, 48, 102-107 and 131-133).

Applicants argue that claims 17, 75-80, 84-86, 88, 89, 92, 93, 128, and 129 as amended have a functional limitation Applicants argue that claim 17 as amended is directed to probes which can identify or isolate an amylase-encoding gene by hybridizing to the gene under specific hybridization conditions. Claim 75 as amended is directed to nucleic acid probes for identifying or isolating an amylase-encoding gene, wherein the probe comprises an oligonucleotide at least about 50 nucleotides in length and having a segment of at least 50 contiguous nucleotides of a nucleic acid of the invention, and which hybridizes under specific hybridization conditions. This is not persuasive because as noted above in the rejection under 112, 2nd paragraph, one can not distinguish functional capabilities of a nucleic acid by hybridization as hybridization is a purely

structural phenomenon; i.e., hybridization occurs between any two nucleic acids which are sufficiently similar to each other to bind under the conditions of the hybridization reaction. For example an DNA consisting of nucleotides 1-100 of SEQ ID NO:125 will hybridize equally well under high stringency conditions to itself (a nucleic acid which **does not** encode an alpha amylase) and to SEQ ID NO:125 (a nucleic acid which **does** encode an alpha amylase). As such for Claim 75 the recited structural features do not correlate to the recited intended use and the "functional limitation" in Claim 17 has been given no patentable weight as this is not a "function" that is determined by structure at all.

Applicants argue in response to the examiner's previous statements that for most of the rejected claims that recited structural features of the genus do not constitute a substantial portion of the genus because the remainder of the structure of a nucleic acid encoding a polypeptide with alpha amylase activity is completely undefined that applicants need not enable or describe unrecited subject matter as encompassed by the term comprising. Applicants state that it is inappropriate for the Office to require Applicants to enable or describe unrecited subject matter as encompassed by the term "comprising" to satisfy the requirement of section 112. However, this is completely incorrect where as in the instant situation it is

this **unrecited** subject matter that necessary to provide the essential features of the claimed subject matter. For the claims to be sufficiently described the structural features recited must be sufficient to provide the functional features otherwise it is left to skilled artisan to fill in the gaps. Most fragments of SEQ ID NOS 125 or 126 or sequences having high structural homology thereto as claimed in claims 10-12, 17, 48, 75-80, 84-86, 88, 89, 92, 93, 102-107, 128, 129 and 131-133 will not by themselves have alpha amylase activity such that it is the **unrecited** subject matter of the claim that is necessary to provide for the recited functional feature.

Claims 1, 6-12, 16, 17, 47, 48, 75-80, 84-86, 88, 89, 92, 93, 102-107, and 122-133 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for polynucleotides encoding SEQ ID NO:126, does not reasonably provide enablement for any polynucleotide having at least 85% sequence identity to SEQ ID NO:125 and encoding a polypeptide with an alpha amylase activity or any polynucleotide comprising at least 50-500 bases of a sequence having 90-99% identity to SEQ ID NO:125, or any polynucleotide comprising a fragment of SEQ ID NO:125, or all fragments and variants thereof or vectors and host cells comprising said nucleic acids. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The rejection is explained in the previous Office Action.

Applicants argue that the Examiner has not met her initial burden to establish a reasonable basis to question the enablement provided. In particular, applicants submit that neither Bork, Van de Loo et al., Broun et al., Witkowski et al. or Seffernick et al. discuss whether or not screening a large number of nucleic acid variants would have constituted undue experimentation to one of skill in the art at the time of the invention. Furthermore, applicants submit that the instant references appear to support the argument that most changes in an enzyme's amino acid sequence are not important in determining or changing its catalytic specificity. Therefore, applicants submit that these references support the idea that most changes in an enzyme's amino acid sequence will result in little or no effect on its specificity or activity. Applicants also submit that the Examiner did not sufficiently consider Dr. Short's declaration and that the arguments and statements made by Dr. Short are sufficient to rebut any possible *prima facie* case of lack of enablement. Applicants assert that in Dr. Short's declaration, he states that it would not have been necessary for one of skill in the art to understand which specific regions or

structural elements of an alpha amylase were required for function or activity to routinely generate the genus of claimed alpha amylase-encoding nucleic acids. According to Dr. Short, enzyme screening technology, such as high throughput screening, makes methods which require previous knowledge of protein structure obsolete and unnecessary. Applicants also argue that the specification provides guidance as to which amino acid substitutions can be made to make the genus of alpha amylase-encoding nucleic acids of the invention.

Applicant's arguments have been fully considered but are not deemed persuasive to overcome the instant rejection. The Examiner acknowledges the amendments to the claims, Dr. Short's declaration, and the teachings of the specification. However the Examiner disagrees with applicant's contention that the claimed invention is enabled by the teachings of the specification. In regard to the references by Bork, Van de Loo et al., Broun et al., Witkowski et al. and Seffernick et al, it is noted that the instant references were introduced in support of the argument that even in cases where the structural homology is high functional annotation is unpredictable absent some knowledge or guidance as to how structure correlates with function. It is reiterated herein that testing the extremely large number of variants encompassed by the claims constitutes

undue experimentation when there is no guidance as to how structure correlates with function. While the argument can be made that one of skill in the art could predict which variants are most likely to encode polypeptides having alpha amylase activity based on structural homology, thus reducing the number of species to test, the instant references, particularly Broun et al., Witkowski et al., and Seffernick et al., show that even in cases where the species in a genus are extremely similar in structure, one cannot assume functional homology.

In addition, while it is agreed that one of skill in the art would certainly expect changes in the catalytic site of an enzyme to have an effect on activity and/or specificity, it is noted that neither Dr. Short nor any references of record teach that **any** amino acid change in the non-catalytic sites of an enzyme will not have an effect on specificity or activity such that a skilled artisan could be assured that changes can be made at these positions. In fact, one of skill in the art would not expect **all** amino acid changes in the non-catalytic sites to have no effect whatsoever on an enzyme since it is well known in the art that amino acid changes in non-catalytic sites may result in changes in the three dimensional structure of a protein such that folding would change to the extent that activity is affected. Furthermore, while the catalytic site of an enzyme is

essential for enzymatic activity, it is noted that amino acids outside the catalytic site often have functions associated to an enzyme's activity and/or substrate specificity such that changes to these regions also often result in substantial changes in the activity of the enzyme. The examiner respectfully disagrees with the notion that Dr. Short's declaration has not been sufficiently considered or that such declaration is sufficient to rebut any possible *prima facie* case of lack of enablement. As previously indicated while the examiner agrees that alpha amylase activity assays are well known in the art, and one could make numerous species encompassed by the claims using well known molecular biology techniques, producing variants useful as alpha amylases requires that one of skill in the art know or be provided with guidance for the selection of which of the infinite number of variants have the activity. Without such guidance, one of skill in the art would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. Guo et al. (PNAS 101(25):9205-9210, 2004) teach that the percentage of random single substitution mutations which inactivate a protein for 3-methyladenine DNA glycosylase is 34% and that this number appears to be consistent with other studies in other proteins as well. Guo et al. further show in Table 1 that the percentage of active mutants for multiple

mutants appears to be exponentially related to this by the simple formula $(.66)^x$ X 100% where x is the number of mutations introduced. Applying this estimate to the instant claims, 85% identity at the nucleic acid level allows up to 209 mutations within the 1395 nucleotides of SEQ ID NO:125 and therefore could result in up to 209 mutations within the 464 amino acids of SEQ ID NO:126 (assuming every alteration in nucleotide sequence resulted in an amino acid change) and even if one assumes that only 50% of nucleotide changes lead to an amino acid change allows up to 105 mutations within the 464 amino acids of SEQ ID NO:126. Applying the estimate produced from the data of Guo et al. to this situation, only $(.66)^{105}$ X 100% or 1.1×10^{-17}% of random mutants having 85% identity to SEQ ID NO:125 would encode active proteins. Current techniques (i.e., high throughput mutagenesis and screening techniques) in the art would allow likely for finding a few active mutants within several hundred thousand or up to about a million inactive mutants (despite even this being an enormous quantity of experimentation that would take a very long time to accomplish) but finding a few mutants within several billion or more as in the instant claims would not be possible. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount

of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification.

In regard to the teachings of the specification, it is noted that contrary to applicant's assertion, nowhere in the specification, including the sections specified by applicants, can one find a teaching or suggestion as to which amino acids in the polypeptide of SEQ ID NO:126 can be modified and obtain homologs having the same alpha amylase activity as that of the polypeptide of SEQ ID NO:126. The sections of the specification indicated by applicants merely define what constitutes a conservative substitution, and a substantially identical amino acid sequence, and presents a statement indicating that polypeptides having alpha amylase activity may have certain amino acids removed and still have the same activity, as well as a statement indicating that one could test these modified polypeptides for alpha amylase activity by a number of methods. Thus, in view of the information provided, the lack of relevant examples, the lack of knowledge regarding the structural elements associated with the required function, and the unpredictability of the art in regard to accurate annotation of function based solely on structural homology, one of skill in

the art cannot reasonably conclude that the specification enables the full scope of the claimed invention.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 10-11, 48, 75, 76, 84-86, 92, and 102-107 are rejected under 35 U.S.C. 102(b) as being anticipated by Tachibana et al. (Reference AK of applicant's IDS).

Tachibana et al. teach the isolation and expression of a polynucleotide encoding *Pyrococcus* sp. KOD1 alpha amylase. This polynucleotide has 80% identity to SEQ ID NO:125 and encodes a protein with 85% identity to SEQ ID NO:126. Furthermore, while the entire gene of Tachibana et al. does not have 85% identity to the entire sequence of SEQ ID NO:125, it comprises a region of 75 nucleotides having greater than 95% identity to the corresponding portion of SEQ ID NO:125 (i.e., residues 1463-1537 of Tachibana et al. have 95% identity to residues 1018-1092 of SEQ ID NO:125) and thus anticipate claims 75, 76, 84-86, and 92. The protein encoded by the gene of Tachibana et al. comprises a region of 149 amino acids having 97% identity (i.e., residues 219-367 of Tachibana et al.) to residues 221-369 of SEQ ID

NO:126 and a region of 76 amino acids having 99% identity (i.e., residues 292-367 of Tachibana et al.) to residues 294-369 of SEQ ID NO:126 and therefore Tachibana et al. anticipates claims 10, 11, 48 and 102-107.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 88 and 89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tachibana et al. (Reference AK). The rejection is explained in the previous Office Action.

Applicant has not presented any arguments specifically traversing this rejection but instead relies upon the traversal discussed above. Therefore, this rejection is maintained for the reasons presented above.

Claims 2-4 are allowed. The gene of Tachibana et al. is not sufficiently similar to the gene of SEQ ID NO:125 to hybridize thereto under the high stringency conditions of the instant claim nor does the art suggest modifications of the prior art gene which would result in a gene within the scope of Claims 2-4.

Claims 14, 15, 134, and 135 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, 2nd paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated

from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca E. Prouty whose telephone number is 571-272-0937. The examiner can normally be reached on Tuesday-Friday from 8 AM to 5 PM. The examiner can also be reached on alternate Mondays

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The fax phone number for this Group is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Rebecca Prouty
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Art Unit 1652